REMARKS

Favorable reconsideration is respectfully requested in view of the amendments and remarks of record and the foregoing remarks and 132 Declaration.

On page 2 of the Office Action of May 22, 2007, claims 3 and 4 were again rejected under 35 U.S.C. § 102 as anticipated by or, in the alternative, under 35 U.S.C. § 103 as obvious over US 5,143,935. Applicants respectfully traverse this rejection, as applied to the amended claims, for reasons of record and for the following reasons.

The present invention is characterized by administering 4-amino-5-chloro-2-methoxy-N-[(2S,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide or an acid addition salt thereof. This stereoisomer has high binding affinity for serotonin receptor 4 ($5HT_4$) and does not cause thrombus formation, arteritis or encephalomalacia. Administration of this stereoisomer improves the movement of the digestive tract.

US Patent 5,143,935 and JP-A-17434/1993 describe that 4-amino-5-chloro-2-methoxy-N-((2S,4S)-1-ethyl-2-hydroxymethyl-4-pyrrolidinyl)benzamide (TKS159), or an acid addition salt thereof, improves the movement of the digestive tract. However, disorders such as thrombus formation, arteritis or encephalomalacia were observed when TKS159 was repeatedly orally administered to a beagle dog during safety testing.

On the other hand, the claimed stereoisomer (TM161) is a metabolite of TKS159 in a beagle dog and unexpectedly does not cause thrombus formation, arteritis or encephalomalacia, and is unexpectedly highly effective in improving the movement of the digestive tract. Thus, the cited art does not suggest the claimed invention because it does not suggest that the claimed stereoisomer has these unexpected properties.

The following experimental data showing that 4-amino-5-chloro-2-methoxy-N-[(25,4S)-2-hydroxymethyl-4-pyrrolidinyl]benzamide hydrochloride (TM161) shows excellent effect as compared with TKS159. The following experimental data was presented in a 132 Declaration submitted March 6, 2007 and indicates that the claimed compound is unexpectedly highly effective in improving the movement of the digestive tract.

A. The action of promoting the movement of the digestive tract

(1) Affinity for serotonin receptor 4 ($5HT_4$)

Test drugs	IC_{50} μM
TM161	0.25
TKS159	0.45

These results indicate that the affinity for serotonin receptor 4 of TM161 is 1.8 times greater than that of TKS159.

(2) Relaxation reaction in rat-extracted sample

Test drugs	IC_{50} μM
TM161	0.7
TKS159	1.1

These results indicate that the relaxation reaction to TM161 in rat-extracted sample is 1.6 times greater than for TKS159.

Thus, applicants submit that it is apparent to a skilled artisan that TM161 is surprisingly and unexpectedly more effective in promoting movement of the digestive tract than TKS159.

Furthermore, in the attached 132 Declaration dated December 20, 2007, Applicants submit results of side-effect and safety testing of a claimed compound as compared to the cited compound. The submitted data shows that the claimed compound unexpectedly does not cause thrombus formation, arteritis or encephalomalacia. Shown below is the data presented in the attached Declaration.

A. Side-effects

The binding affinity for TM161 and TKS159 for the dopamine D2 receptor

Test drugs	IC_{50} μM
TM161	34
TKS159	3.8

These results indicate that the binding affinity of TM161 is 8.9 times greater than that of TKS159. Binding with dopamine D2 receptor is a cause of side-effects, such as extrapyramidal sign.

B. Safety

TM161 was administered orally to three beagle dogs at a dose of 100 mg/kg once a day for 4 weeks.

Pathohistological tests were performed using a light microscope and abnormalities were not found. Further, neither thrombus formation, arteritis nor encephalomalacia was identified.

On the other hand, TKS159 was administered orally to three beagle dogs at a dose of 30 mg/kg once a day for 4 weeks.

Pathohistological tests were performed using a light microscope and abnormalities were not found. Further, neither thrombus formation, arteritis nor encephalomalacia was identified.

Applicants therefore note that TM161 can be administered in a 3.3 times larger dose than TKS159 without engendering side effects.

D. Conclusion

Thus, applicants submit that the '935 patent fails to suggest the claimed invention because it fails to teach the above noted unexpected effects. Applicants further note that, as indicated in part 1 of the December 11, 2007 amendment and reply, this reference fails to teach the claimed invention and therefore cannot inherently teach such unexpected effects.

Applicants therefore suggest that, for the above noted reasons, this rejection is untenable and should be withdrawn.

In view of the foregoing and the remarks and amendments of record, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,
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